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(54) **Antihypertensive composition containing indapamide and a thiachroman**

(57) The present invention provides pharmaceutical compositions and preparations comprising a combination of indapamide and certain thiachromans, especially 8-(3-tert.-butylamino-2-hydroxypropoxy)-thiachroman, or a physiologically tolerable acid addition salt thereof. Each of the two components may be in the racemic form or in the form of an optical isomer. The components in combination have unexpected synergistic properties and can be used for treating hypertension.

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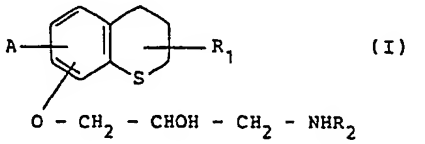
SPECIFICATION

Synergistic antihypertensive pharmaceutical composition

The present invention relates to a pharmaceutical composition comprising a combination of active substances.

Indapamide, or N-(3-sulphamoyl-4-chlorobenzamido)-2-methylindoline, also known as 4-chloro-N-(2-methyl-1-indolinyl)-3-sulphamoylbenzamide, has been described in Example 1 of GB 1,203,691 (FR 69.06023; published under No. 2,003,311) as a diuretic that can be used especially for the treatment of arterial hypertension.

GB Patent 1,308,191 (FR 71.11445; published under No. 2,092,004) describes and claims (3-amino-2-hydroxypropyloxy)thiachromans of the general formula



(I)

wherein

A represents a hydrogen or halogen atom,

R_1 represents a hydrogen atom or an alkyl radical having from 1 to 5 carbon atoms, and

R_2 represents an alkyl radical having from 1 to 5 carbon atoms or a cycloalkyl radical having from 3 to 6 carbon atoms,

and salts thereof with mineral and organic acids. This patent mentions cardiovascular properties, especially *beta*-blocking properties. 8-(3-tert.-butylamino-2-(hydroxypropoxy)-thiachroman (and the hydrochloride salt thereof) is described in Example 2 of the above British Patent. For the sake of convenience, 8-(3-tert.-butylamino-2-hydroxypropoxy)-thiachroman will be referred to hereinafter as "THPT".

We have now found that combinations of the above-mentioned compounds, in particular indapamide and THPT, have unexpected synergistic properties.

The combinations may be used for the treatment of hypertension.

The present invention provides a pharmaceutical composition which comprises indapamide and a thiachroman of the general formula I shown above, wherein

A represents a hydrogen or halogen atom,

R_1 represents a hydrogen atom or an alkyl radical having from 1 to 5 carbon atoms, and

R_2 represents an alkyl radical having from 1 to 5 carbon atoms or a cycloalkyl radical having from 3 to 6 carbon atoms,

or a physiologically tolerable addition salt thereof.

Preferably the thiachroman of the general formula I is THPT.

Accordingly, the present invention especially provides a pharmaceutical composition which comprises a combination of indapamide and THPT or a physiologically tolerable addition salt thereof.

The composition may be a simple admixture of compounds, or the active ingredients may, for example, be formulated with a pharmaceutically suitable carrier into a form suitable for direct administration.

Thus, the present invention also provides a pharmaceutical preparation which comprises indapamide in admixture or conjunction with a thiachroman of the general formula I given above, especially THPT, or a physiologically tolerable addition salt thereof, and in admixture or conjunction with a pharmaceutically suitable carrier. The pharmaceutical preparation may, for example, be in dosage unit form.

One or more of the thiacromans may be present in the composition or preparation.

Each of the active ingredients, independently of the other(s) may be in racemic form or in the form of an optical isomer, and indapamide, for example, may be in the form of its hemi-hydrate. Each compound may also be in the form of a salt of addition with a mineral or organic acid.

Suitably the ratio of indapamide to the thiochroman or salt thereof (preferably THPT or salt thereof) is, for example, from 1:15 to 1:1 by weight, more especially substantially 1:4.

The pharmaceutical compositions or preparations of the present invention are preferably administered by the oral route and may be, for example, in the form of tablets, coated tablets, capsules or suspensions. Preferably they contain from 0.8 to 3 mg of indapamide and from 3 to 12 mg of the thiachroman, especially THPT, or a physiologically tolerable addition salt thereof. Excipients or carriers customary for oral forms may, for example, be used. The combinations may be administered for example in one or two daily doses.

Although the indapamide and the thiachroman are preferably administered simultaneously, they may be taken one immediately after the other or, having regard, for example, to the half-life *in vivo* after absorption, at intervals such that a synergistic action of the two components in the body is achieved. For this, the components may be brought together in the form of a pack, which comprises a container or other support member holding the indapamide and the thiachroman specified above, or a physiologically tolerable salt

thereof, together with indications and/or instructions to indicate or facilitate one or more treatments each comprising the administration of indapamide and the thiachroman or salt thereof simultaneously or at close intervals sufficient to obtain a synergistic effect. In the pack there may be pharmaceutical preparations containing a combination of the active ingredients or preparations containing the two ingredients separately.

The following test illustrates the synergistic effect of a combination of the present invention.

Pharmacological study.

Indapamide and THPT were tested, alone and in combination, for functional inhibition of membrane adenylate cyclase.

The red corpuscles of pigeons have been known for their considerable adenylate cyclase activity since the studies of SUTHERLAND *et al.* (Adenyl cyclase 1. Distribution, preparation and properties, J. Biol. Chem. (1962) 237 : 1220-1227). The experiments were carried out on erythrocyte ghosts (open cells) prepared from the blood of Strasser pigeons according to the method of SALESSE R. and GARNIER J., "Effects of drugs on pigeon erythrocyte membrane and asymmetric control of adenylate cyclase by the lipid bilayer" (Biochem. Biophys. Acta (1979) 554 : 102-103).

The suspension obtained were incubated for twenty minutes in hypotonic buffer with a volume of the tested product at the final concentration desired. The adenylate cyclase activity was determined according to the method of BIRNBAUMER L. *et al.* (J. Biol. Chem. (1969) 244 : 2468-3476) and RAMACHANDRAN J.; LEE V. (Biochem. Biophys. Res. Commun. (1970) 41 : 358-366).

The final concentrations of reagents were ATP 2 mM having 1μCi of [α-^{32}]P ATP, theophylline 4 mM, phosphocreatine 10 mM, creatine kinase 0.5 g/litre, $MgCl_2$ 7.5 mM, tromethamine HCl ("TRIS" HCl) 10 mM, pH = 7.4.

The total volume was 75 microlitres and the number of cells per tube was approximately 10^8.

The production of cyclic AMP (cAMP) was stimulated either by 0.05 mM of isoproterenol in the presence of 0.1 mM of GTP, or by 10 mM of sodium fluoride. The compound was added to the final concentration required.

The reaction was stopped after 15 minutes at 37°C by adding 300 microlitres of 0.5 N hydrochloric acid and by placing the mixture over a boiling water bath for 3 minutes. The tubes were then removed from the water bath and the contents were neutralised by 300 microlitres of 1.65 N imidazole.

After centrifugation (10 minutes, 4000 g), 500 microlitres of the supernatant solution were poured into a neutral activated alumina column and were eluted with 2.6 ml of imidazole, 10 mM, pH = 7.5. These columns had a yield of cAMP of 95 %.

The radioactivity of the samples was measured in a scintillation counter "Packard Tricarb", using the Cerenkov effect after adding 10 ml of 1 % aqueous solution of 7-amino-1,3-naphthalenedisulphonic acid to the eluate (counting yield 65%).

According to a logarithmic scale, there were determined three concentrations above and three concentrations below the concentration for which, *in vitro*, on the mesenteric artery of rats an inhibition of half of the vasoconstriction induced by nopadrenaline could be observed.

The results were calculated as the average of three tests in picomoles of cyclic AMP produced per minute and per milligramme of membrane phospholipids.

It was seen that the indapamide and THPT subjected to this test inhibited the activation of adenylate cyclase stimulated by isoproterenol or sodium fluoride since the quantity of cAMP produced decreased. The nature of the effect on the production of cAMP which was observed was dependent on the concentration of the compound used.

The active concentration of each compound producting an inhibition of 25 % (AC_{25}) and 50 % (AC_{50}) was determined graphically. These concentrations were as follows:

Indapamide (m.w. = 365.89) : $AC_{25} = 9 \times 10^{-5}$ mole/litre
$AC_{50} = 3 \times 10^{-4}$ mole/litre

THPT HCl (m.w. = 331.90) : $AC_{25} = 1.2 \times 10^{-5}$ mole/litre
$AC_{50} = 7 \times 10^{-5}$ mole/litre

The inhibition produced by the mixtures of the two compounds at those concentrations was then measured. The following Table shows the percentage inhibition obtained with each of the 4 mixtures:

TABLE

	Indapamide 25 %	Indapamide 50 %
THPT 25 %	45 %	62 %
THPT 50 %	62 %	75 %

It can be seen that the inhibition obtained with the mixture of the two compounds is clearly superior to that obtained with each compound separately. For example, with a mixture at the concentration of 9×10^{-5}

mole/litre of indapamide and 1.2×10^{-5} mole/litre of THPT, 45 % inhibition is obtained, whereas with the single ingredients this inhibition is only achieved by 2.5×10^{-4} mole/litre of indapamide or by 5×10^{-5} mole/litre of THPT; that is approximately 3 to 4 times the quantity is necessary for each of the compounds taken separately. The two effects corresponding to 25 % inhibition are therefore multiplied in their global effect and result in a 45 % inhibition of the activity of the enzyme.

Discussion :

Since THPT is known as a *beta*-blocker, its inhibitory activity on adenyl cyclase associated with an extracellular *beta*-receptor might be foreseen. However, it was not to be expected that an antihypertensive diuretic such as indapamide would have a similar activity and that, above all, the activity of these two compounds would be combined: in fact, the dose/activity curve of these compounds, and especially their AC_{25} and AC_{50}, show that they act in multiplying synergism.

cAMP is a second intracellular messenger triggering the start of cellular functions. By inhibiting adenyl cyclase, all states of cellular hyperactivity, such as those existing in hyperactivity of the thyroid, hypertension, hypersensitivity, etc., are slowed down. As a result, the combination of the two compounds acting in synergism according to the invention is indicated especially for treating states of *beta*-dependent hyperactivity such as are encountered in hypertension, especially in cases of severe arterial hypertension together with renal insufficiency, or in disorders such as hyperactivity of the thyroid.

The present invention also provides a pharmaceutical composition comprising indapamide and the thiochroman specified above, or a physiologically tolerable salt thereof, especially indapamide and THPt or physiologically tolerable salt thereof, for use in treating hypertension.

The following Examples illustrates the composition of a pharmaceutical preparation of the present invention.

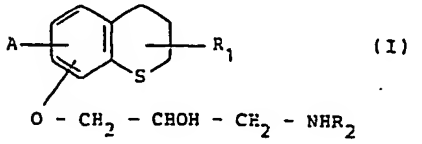
Example: 90 mg TABLET

Indapamide	1.25 mg
8-(3-tert.-butylamino-2-hydroxypropoxy)-thiachroman hydrochloride	5.00 mg
stearic acid	0.90 mg
sodium carboxymethyl starch	3.00 mg
microcrystalline cellulose	33.38 mg
lactose	35.75 mg
calcium hydrogen phosphate	10.00 mg
colloidal silica	0.27 mg
magnesium stearate	0.45 mg

This tablet may be coated.

CLAIMS

1. A pharmaceutical composition which comprises
   (i) indapamide, and
   (ii) a thiachroman of the general formula



(I)

wherein

A represents a hydrogen or halogen atom,

R_1 represents a hydrogen atom or an alkyl radical having from 1 to 5 carbon atoms, and

R_2 represents an alkyl radical having from 1 to 5 carbon atoms or a cycloalkyl radical having from 3 to 6 carbon atoms,

or a physiologically tolerable acid addition salt thereof.

2. A pharmaceutical composition which comprises

(i) indapamide, and

(ii) 8-(3-tert.-butylamino-2-hydroxypropoxy)-thiachroman or a physiologically tolerable acid addition salt thereof.

3. A pharmaceutical composition as claimed in claim 1 or claim 2, wherein the ratio of indapamide to thiochroman or salt thereof is from 1:15 to 1:1 by weight.

4. A pharmaceutical compositions as claimed in claim 3, wherein the ratio of indapamide to thiochroman or salt thereof is substantially 1:4 by weight.

5. A pharmaceutical preparation which comprises

(i) indapamide,

in admixture or conjunction with

(ii) a thichroman of the general formula I specified in claim 1, wherein A, R_1 and R_2 have the meanings given in claim 1, or a physiologically tolerable acid addition salt thereof,

and in admixture or conjunction with a pharmaceutically suitable carrier.

6. A pharmaceutical preparation which comprises

(i) indapamide, and

(ii) 8-(3-tert.-butylamino-2-hydroxypropoxy)-thiachroman or a physiologically tolerable acid addition salt thereof,

in admixture or conjunction with a pharmaceutically suitable carrier.

7. A pharmaceutical preparation as claimed in claim 5 or claim 6, wherein the ratio of comonent (i) to component (ii) is as specified in claim 3 or claim 4.

8. A pharmaceutical preparation as claimed in any one of claims 5 to 7, which is in a form suitable for oral administration.

9. A pharmaceutical preparation as claimed in any one of claims 5 to 8, which is in dosage unit form.

10. A pharmaceutical preparation as claimed in claim 9, which contains from 0.8 to 3 mg of indapamide and from 3 to 12 mg of 8-(3-tert.-butylamino-2-hydroxypropoxy)-thiachroman or salt thereof.

11. A pharmaceutical preparation as claimed in claim 10, which contains substantially 1.25 mg of indapamide and substantially 5 mg of 8-(3-tert.-butylamino-2-hydroxypropoxy)-thiachroman or salt thereof.

12. A pharmaceutical preparation as claimed in claim 5, substantially as described in the Example herein.

13. A pack which comprises a container or other support member holding indapamide and a thiachroman of the general formula I shown in claim 1, in which A, R_1 and R_2 have the meanings given in claim 1, or a physiologically tolerable acid addition salt thereof, together with indications and/or instructions to indicate or facilitate one or more treatments each comprising administratin of indapamide and the thiachroman or salt thereof simultaneously or at close intervals sufficient to obtain a synergistic effect.

14. A pack as claimed in claim 13, wherein the thiachroman or salt thereof is 8-(3-tert.-butylamino-2-hydroxypropoxy)-thiachroman or a physiologically tolerable salt thereof.

15. A pharmaceutical composition as claimed in claim 1, for use in the treatment of hypertension.

16. A pharmaceutical composition as claimed in claim 2, for use in the treatment of hypertension.

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